

### **REMARKS**

Reconsideration of this application is requested.

The applicant responds as follows to the various issues raised by the Examiner using the Examiner's headings.

#### **Information Disclosure Statement**

1. The Examiner's comments have been noted. The publications referred to in the applicant's specification (page 6, lines 36-38 and page 7, lines 21-23) are references which are well-known in the art and generally available. Furthermore, these publications are not considered relevant to assessing the patentability of the applicant's claims. In the circumstances, it is not thought necessary or appropriate to include these in an information disclosure statement.

#### **Specification**

2. The specification has been amended to indicate the national phase nature of the present case based on PCT/GB03/001161 and to make reference to the earlier-filed provisional application.

3. The specification has been carefully reviewed and it is thought to meet the requirements of Section 112, 1st paragraph. With regard to the specific examples referred to by the Examiner, as far as the term "An 18-mer fully protected phosphorothioated deoxyribonucleotide containing 66% full length product was purified 5'-dimethoxytrityl on using the method of Example 1 ..." is concerned, the applicant respectfully submits that the language is grammatically correct and understandable to one in the art. Thus, the language refers to a sample of the stated material which has a purity of the specified level. It is commonplace to refer to materials by their main component, and then specify the purity, i.e. the actual amount of the named material present.

As far as the grammar is concerned, this is believed to be completely clear and appropriate. The Examiner seems to have a problem with the reference to "was purified 5'-dimethoxytrityl on". However, this is a commonly-used approach in the oligonucleotide purification field and would be readily understood by one of ordinary skill in the art. It refers to the practice of purifying the oligonucleotide without removing the

trityl protecting group, as opposed to "purification trityl off". There is no lack of clarity or verbosity, and the grammar is thought to be appropriate. Accordingly, the Examiner is requested to reconsider and withdraw the Section 112, 1st paragraph objection to the specification.

4. A corrected Abstract on a separate sheet is attached hereto.
5. The specification has been amended to capitalize trademarks. Generic terminology for the products identified by trademarks is included.

#### **Claim Objections**

6. The applicant does not understand the Examiner's objection to claim 8. The applicant's copy of claim 8 does not include a period after "claim" in line 1. Reconsideration or clarification of the Examiner's position is requested..

#### **Claim Rejections – 35 U.S.C. 1.12**

7. The Examiner is requested to reconsider the Section 112, 2nd paragraph rejection of claims 4, 5, 13, 22 and 27. The applicant respectfully submits that the language of the claims is clear and definite and that the invention is particularly pointed out and distinctly claimed.

The Examiner has objected to the terms "substantially free of" in claims 4 and 27; "substantial increase" in claims 5 and 27 and "sufficient amount" in claim 22 as relative terms which render the claims indefinite. The Examiner dismisses the applicant's discussion of these terms in the specification at pages 3 and 12 as not providing "a standard for ascertaining the requisite degree of" these terms.

The applicant respectfully submits that the claim language questioned by the Examiner is clear and definite. Claims are to be read with the skill of the art and there cannot be any doubt as to what the applicant means by the claim language, particularly with the discussion provided in the applicant's specification. Claim language cannot be read in a vacuum or in the absence of the knowledge of one of ordinary skill in the art.

The applicant submits that the terms "substantially free of", "substantial increase" and "sufficient amount" would be perfectly well understood by one of ordinary skill in the art, who would have no difficulties in determining the metes and bounds of such terms. This sort of language is consistently accepted and approved by the USPTO and,

significantly, the Examiner has given no relevant authority to support his objections. The language "substantially free of" reflects the virtual impossibility of providing a solution which is totally free from metal salts, and the ease by which a claim to "free from" might be evaded, by simply adding an insignificant amount of metal salts. Similar comments apply with respect to the other terms queried by the Examiner although it is noted that the reference to "sufficient amount" in claim 22 is further qualified in context as sufficient "to cleave said 5'-O-trityl protecting group". Clearly, one in the art would have no problem understanding what the language "a sufficient amount" means in the context of claim 22. The same conclusion is true with respect to the other terms. Accordingly, reconsideration and withdrawal of the objection to the above-noted terms is requested.

The Examiner is also requested to reconsider the object to the language "linear manner". Surely there cannot be anything uncertain about this language and one skilled in the art would know exactly what the applicant intends. The term "linear manner" is a wholly standard term of art which, of course, means that the pH increases by a set amount over a given time interlude, such that the graph of pH versus time is a straight line. As noted, this would be well understood by one in the art. Hence the term should be acceptable.

For the reasons noted, the Examiner is requested to reconsider and withdraw the Section 112, 2nd paragraph rejection of claims 4, 5, 13, 22 and 27.

The Examiner is also requested to reconsider the rejection of claims 1-27 under Section 112, 2nd paragraph as being incomplete in omitting essential steps. The Examiner states, in this regard, that "the omitted steps are: how the solution in step 1b is increasing in pH in time". However, one in the art would readily understand how this is done. It is trivial to achieve such a change, for example, by adding base to the solution, or by increasing the ratio of higher pH buffer to lower pH buffer employed in the solution passing through the column. This would readily be understood by one skilled in the art.

#### **Claim Rejections – 35 U.S.C. 102**

8. The Examiner is requested to reconsider the Section 102(b) rejection of claims 1, 5-7, 10, 12-14, 16-18 and 25 as anticipated by Lu et al. (1994). The reference does not disclose the applicant's invention as defined in the rejected claims.

Lu discloses a process for the separation of very short oligonucleotides by the use of anion exchange chromatography. However, Lu does not disclose, nor does Lu in any way suggest, the use of a titratable anion exchange composition as required by the claims of the present invention. Lu employs a quaternary amine anion exchange resin (see paragraph 2.1 of Lu). Such resins comprise a permanent positive charge by virtue of their chemical structure and are therefore incapable of losing a positive charge as pH increases. Lu teaches the use of titratable ring protons on thymine or guanosine base moieties (see Abstract), i.e. it is the oligonucleotide which is titratable, not the resin. This is manifestly not a disclosure of the use of a titratable anion exchange resin. The claims of the present invention are, therefore, novel over Lu.

In the circumstances, the applicant submits that withdrawal of the Section 102(b) rejection based on Lu is in order and is requested.

**Claim Rejection – 35 U.S.C. 103**

9. The Examiner is requested to reconsider the Section 103(a) rejection of claims 4, 8 and 15 as unpatentable over Lu et al. considered with Asteriadis et al. as set out in Section 9 of the action. The Examiner is also requested to reconsider the Section 103(a) rejection of claims 2, 8 and 11 based on Lu et al. in view of Jin-Yan et al.; the Section 103(a) rejection of claims 3 and 9 as unpatentable over Lu et al. in view of Crane et al.; the Section 103(a) rejection of applicant's claims 19, 20-23, 26; the Section 103(a) rejection of claim 24 and the Section 103(a) rejection of claim 27, all based on Lu et al. with secondary references. See Sections 10-15 of the action. The applicant's claims as rejected on Lu et al. with secondary references are not in any sense obvious from the Examiner's references. The secondary references do not fill in the substantive deficiencies noted above with respect to Lu. Furthermore, there is no motivation in the references, no matter how considered, to reach the applicant's invention as defined in the claims.

More specifically, there is no teaching in Lu that would motivate one of ordinary skill in the art to consider the process of the present invention. Lu contains no hint or suggestion that would cause the skilled person to abandon the key teaching of Lu concerning the need for the use of a quaternary (non-titratable) anion exchange resin in favor of the resins employed in the process of the present invention. It is submitted that

it would be perverse of the skilled person to take such a step given the clear teaching of Lu. Accordingly, applicant's main claim 1 would not, in any sense, be obvious to the skilled person over the teaching of Lu. It therefore follows that the remaining claims, which each depend upon claim 1, would not be obvious over Lu, either alone or in combination with any of the references cited by the Examiner.

**Double-Patenting**


16. The Examiner is requested to reconsider the rejection of claims 1-27 as unpatentable for obviousness-type double-patenting in view of claims 1-26 of U.S. Appln. No. 10/159,322. It is respectfully submitted that the present claims are not obvious from the claims of Appln. No. 10/159,322.

In making the double-patenting rejection, the Examiner has apparently assumed that the present case and Appln. No. 10/159,322 are commonly assigned. However, this is not the case. The present application is assigned to Avecia Limited while Appln. No. 10/159,322 is apparently assigned to Applied Biosystems. Ownership is thus different although there is a common inventor (Jack Johansen). In the circumstances, it is submitted that a double-patenting rejection is not appropriate. However, more significantly, it is clear that patentably different subject matter is being claimed in the two cases. Thus, it appears from the published version (2003/0091988) of Appln. No. 10/159,322 that the invention claimed therein relates to a method of sequencing an oligonucleotide. This has nothing to do with the method of purifying oligonucleotides of the present invention. The claims of Appln. No. 10/159,322 do not suggest the method of the present invention. Thus, in short, the respective sets of claims are drawn to different and patentably distinct subject matters. In the circumstances, it is submitted that the Examiner's rejection based on Appln. No. 10/159,322 should be withdrawn.

Consistent with the foregoing, the applicant requests that the Examiner reconsider and allow this application.

Favorable action is requested.

Respectfully submitted,  
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